REMARKS

Claims 18 through 34 are pending.

Claims 18 and 19 have been amended to recite that the one or more assay locations and array locations, respectively, comprise a plurality of discrete sites. Support for the amendment can be found in the specification, for example, at page 8, lines 13-14, which discloses that the assay locations or the array locations can comprise a plurality of discrete sites. Claims 18 and 19 also have been amended to indicate that the discrete sites each contain no more than one microsphere. Support for the amendment can be found in the specification, for example, at page 24 lines 1-4, which teaches that the discrete sites of an array can contain one bead or can be empty.

Claim 19 has further been amended to recite that at least one assay location is in fluid contact with at least one array location. Support for this amendment can be found in the specification, for example, in figures 1A-1F, and in the specification at page 10, lines 15-32, which discloses individual sample-containing assay locations in fluid contact with individual array locations.

Claim 20 has been amended to recite that each of the assay locations comprises a library of bioactive agents. Support for this amendment can be found in the specification, for example, at page 13, lines 29-31, which teaches that libraries of bioactive agents can be used in the method of the invention.

Claim 24 has been amended to recite that each microsphere in the subpopulations comprises an identifier binding ligand that will bind a decoder binding ligand, where the bioactive agent is identified by the identifier binding ligand binding to the decoder binding ligand. Support for the amendment can be found in the specification, for example, at page 18, lines 34-37, which indicates that microspheres can comprise identifier binding ligands that bind decoder binding ligands to facilitate identifying bioactive agents.

New claims 33 and 34 are directed to the method of claim 20, where at least a first and

second of said assay locations contain the same library of bioactive agents (claim 33) or different libraries of bioactive agents (claim 34). Support for claims 33 and 34 can be found in the specification, for example at page 7, lines 3-14, which discloses that a composite array can have arrays that are identical or different, and at page 13, line 29 which teaches that a library of bioactive agents can be used.

Rejection under 35 U.S.C. § 112, second paragraph

Applicants respectfully traverse the rejection of claims 18 to 32 as indefinite under 35 U.S.C. § 112, second paragraph. In providing the basis for the rejection, the Office Action lists nine points.

1. Claims 18-32 are allegedly indefinite because the sizes of the recited microspheres are not definitively claimed. Applicants respectfully submit that the methods of claims 18-32 do not require a particular minimum or maximum microsphere size, and that the specification teaches one skilled in the art to determine the appropriate size according to the intended use of the microsphere. For example, the specification at page 11, line 36 through page 12, line 5 teaches that the microsphere can be any of a variety of sizes, and that key to the use of the microsphere is the microsphere/substrate pairing on discrete sites of the substrate. Thus, one skilled in the art would know to select a microsphere size that resulted in discrete distribution of the microspheres on the substrate. It is not necessary for a claim to recite a numerical range if one skilled in the art could determine the scope of the claim from the teachings of the specification. *In re Mattison and Swanson,* 184 USPQ 484 (CCPA 1975). Accordingly, Applicants respectfully request that the Examiner remove this ground for rejection.

2. Claims 18-32 are allegedly indefinite because independent claims 18 and 19 do not indicate the number of microspheres present in discrete sites of the substrate. Claims 18 and 19 have been amended herein to indicate that the discrete sites each contain no more than one microsphere. Accordingly, Applicants submit that claims 18 and 19 as amended clearly indicate the number of microspheres that can be present in discrete sites. Applicants therefore respectfully request that the Examiner remove this ground for rejection.

3. Claims 19 and 25-32 stand rejected as indefinite because the language in claim 19 is allegedly unclear how many "discrete sites" are present in an "array location". The Office Action states that it is interpreting the language of claim 19 to indicate that each "assay location" comprises one or more sites. Applicants, not intending to change the meaning of the statement in the Office Action, presume that the Office Action intended to state that it is interpreting the language of claim 19 to indicate that each "array location" comprises one or more sites. In order to further clarify this matter, Applicants have amended claim 19 to indicate that the recited array location comprises a plurality of discrete sites. In view of the amendment to claim 19, Applicants submit that this claim is not indefinite in view of this issue.

4. Claim 20 further stands rejected because it recites the term "substantially similar". In this regard, Applicants have amended claim 20 to remove the term "substantially similar" and to replace therewith "library". Such bioactive agents include synthetic and natural biomolecules, proteins, peptides and nucleic acids, as taught in the specification, for example, at page 12, lines 30-31, page 13 lines 11-12, page 13 lines 18-20, and page 14 lines 9-10. Applicants submit that the foregoing amendment is clear and definite in view of the teachings of the specification.

5. Claims 23 and 27 are allegedly indefinite for being ambiguous whether use of the phrase "capable of identifying said bioactive agent" is meant to include in the claim identifying the bioactive agent using an optical signature. Applicants submit that recitation in a claim of a functional limitation to subpopulations does not require use of that property in every embodiment of a claim. For example, claims 23 and 27, as they currently stand, encompass methods using the optical signature for identifying the bioactive agent and also encompass methods not using the optical signature for identifying the bioactive agent. Accordingly, Applicants maintain that claims 23 and 27 are clear and definite as written.

6. Claim 24 stands rejected as unclear whether an identifier binding ligand is attached to every microsphere. In this regard, claim 24 has been amended to now recite that at least a first and second microsphere in the subpopulations comprise an identifier binding ligand. In view of the amendment, Applicants respectfully request that this ground for rejection of claim 24 be removed.

B

7. Claim 24 further stands rejected as unclear whether the method includes elucidation of the bioactive agent. Claim 24 has further been amended to indicate that the bioactive agent is identified by the identifier binding ligand (IBL) binding to the decoder binding ligand (DBL). Applicants submit that, as amended, claim 24 is clear and definite.

8. Claims 19 and 25-32 stand rejected as indefinite for not reciting how the first substrate is configured with respect to the second substrate. In this regard, claim 19 has been amended to indicate that at least one assay location is in fluid contact with at least one array location.

This added requirement of fluid contact demonstrates the structural relationship between the first and second substrates. For example, this amendment requires that the first and second substrates both contact the sample. In view of the present amendment and the teachings of the specification, Applicants submit that one skilled in the art can recognize the scope of the claimed invention.

9. Claims 19 and 25-32 are rejected as incomplete for omitting the essential structural relationship of the first and second substrates. In view of the amendment to claim 19 discussed above, claim 19 now recites a structural relationship between the first and second substrates, namely fluid contact with one another. Accordingly, Applicants submit that claim 19, as amended is clear and definite.

Rejection under 35 U.S.C. § 102 as anticipated by Walt et al.

Applicants respectfully traverse the rejection of claims 18, 20, 22, 23 and 28-32 under 35 U.S.C. § 102 as anticipated by Walt et al. U.S. Patent No. 6,023,540.

Walt et al. discloses an optical fiber bundle sensor having wells etched in the end of the bundle into which microspheres can be affixed. Presence of an analyte can be determined by a change of the microsphere's optical signature in the presence of the analyte.

Independent claim 18 is directed to a method of determining the presence of one or more target analytes in one or more samples by contacting the sample with a population of

B

microspheres and with a surface containing a plurality of assay locations which themselves contain discrete sites, and then determining the presence of the target analyte.

As suggested in the Office Action, the recited assay location of claim 18 corresponds to the optical fiber bundle of Walt et al., and the recited discrete sites of claim 18 correspond to the wells etched into the bundle. However, the Office Action has not indicated that Walt et al. teaches the recited surface comprising a plurality of assay locations of claim 18. Moreover, Applicants contend that the recited surface of claim 18 is not explicitly taught in Walt et al.

To anticipate a claim, a prior art reference must teach every element of the claim. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1050, 1053 (Fed. Cir. 1987). Since the Office Action has not pointed to the portion of Walt et al. which teaches the recited surface of claim 18, Applicants submit that the Office Action has not established a *prima facie* case for the lack of novelty of claim 18 in view of Walt et al. Furthermore, Applicants maintain that Walt et al. does not teach the recited surface of claim 18, and, therefore, Walt et al. cannot anticipate the invention of claim 18.

Further regarding claim 28, this claim depends from independent claim 19, which is not rejected under 35 U.S.C. § 102. Because independent claim 19 does not stand rejected under this statute, claim 28 dependent therefrom, which further limits the scope of independent claim 19, cannot stand rejected 35 U.S.C. § 102.

Rejection under 35 U.S.C. § 103(a) as obvious over Walt et al. in view of Geysen et al.

Claims 18-32 stand rejected under 35 U.S.C. § 103 as obvious over Walt et al. U.S. Patent No. 6,023,540, Geysen U.S. Patent No. 5,763,175, and Brenner U.S. Patent No. 5,763175.

Walt et al. is described above.

Geysen describes use of a library of hexapeptide sequences from a particular protein to detect antigen-antibody binding in a method for determining antigenically active peptides.

B

Specifically, Geysen uses a 12 x 8 grid of peptide sequences attached to rods in such a way as to correspond to a microtiter plate. It is Applicants' understanding that the method of Geysen requires use of a single, different peptide sequence on each of the plurality of rods used in the method. Used in this manner, the one or more rods to which antibody binds will correspond to antigenically active peptides according to the respective sequence of the peptide attached to each rod.

Brenner describes a method for sequencing polynucleotides using oligonucleotide tags and tag complements on an array. The array contains spatially addressable locations on a solid support.

Basically the Examiner suggests that the claims are obvious over Walt et al. for the same reasons set forth in the rejection under 35 U.S.C. § 102, stated above. The Examiner suggests that it would have been obvious to use more than one fiber optic array and that the use of vessels to contain sample solutions would have been within the abilities of one of ordinary skill in the are as evidenced by Geysen. Appellants respectfully traverse.

Applicants note that there are three requirements to establish a *prima facie* case of obviousness. These include that "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." (MPEP § 2143).

Applicants respectfully submit that neither Walt et al., nor the knowledge available to one skilled in the art, provides the motivation to practice the invention as claimed in independent claims 18 and 19.

Regarding claims 18, 20, 22, 23 and 29-32, the Office Action indicates that such claims are obvious over Walt el al. for the reasons set forth in the rejection under the above-discussed 35 U.S.C. § 102 rejection. Applicants submit that claims 18, 20, 22, 23 and 29-32 are unobvious in view of Walt et al.

As discussed above regarding the rejection under U.S.C. § 102, Walt et al. does not teach the recited surface comprising a plurality of assay locations of claim 18. The Office Action does not indicate the motivation for one skilled in the art to combine a surface comprising a plurality of assay locations with the teachings of Walt et al. to arrive at the invention of claim 18 and claims dependent therefrom. The mere fact that a reference can be modified does not render the resultant modification obvious unless the prior art also provides the motivation to modify the reference to arrive at the claimed invention. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP § 2143.01.

Even assuming, *arguendo*, motivation to modify Walt et al. in some manner, the Office Action does not indicate that the obvious modification by one skilled in the art would be a combination of a surface comprising a plurality of assay locations with the teachings of Walt et al. To establish a *prima facie* case of obviousness, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (CCPA 1974); MPEP § 2143.03. Because the Office Action has not presented all elements of claim 18 in the obviousness rejection, Applicants submit that there has not yet been established a *prima facie* case for rejection of claims 18, 20, 22, 23 and 29-32 as obvious over Walt et al.

Regarding claim 19 (and, presumably, claims dependent therefrom), it appears that the Office Action is making a rejection under 35 U.S.C. § 103 based on the single reference Walt et al. and is providing Geysen as evidence of skill in the art. No further reference has been made to the Brenner. As such, it does not appear that this is a rejection based on the combination of the Walt et al., Geysen and Brenner. In the rejection, the Office Action states that, in view of the teachings of Walt et al. and what was within the ability of the skilled artisan, it would have been obvious to use more than one fiber optic array in order to scale up the number of analytes that could be simultaneously screened in a vessel such as a microtiter plate.

Applicants maintain that the knowledge available to one skilled in the art as illustrated in Geysen does not teach or suggest the claimed method of adding a sample to a first substrate comprising a plurality of assay locations and contacting the sample with a plurality of array locations comprising discrete sites and with at least two subpopulations of microspheres.

B

Elements from the teachings of Walt et al. cannot be modified or combined with elements drawn from knowledge in the art as exemplified in Geysen, unless there is motivation to do so. If one skilled in the art were to use the optical fiber bundle of Walt et al. in a method such as the art-known method exemplified in Geysen, the result would be the use of an array location (fiber bundle in Walt et al., rod in Geysen) in detecting the binding of a target analyte (antibody in Geysen) by attaching to the array location a single type of probe (microbead in Walt et al., single-sequence peptide in Geysen).

One skilled in the art seeking to employ a method similar to that illustrated in Geysen would not think to use the two or more probe subpopulations recited in claim 19 in order to detect the binding of the target analyte. In Geysen, the one or more rods to which antibody binds correspond to antigenically active peptides according to the respective sequence of the peptide attached to each rod. Accordingly, if each rod were identical, the method of Geysen would fail. Furthermore, if each of the rods contained two or more sequences no definite identification of antigenically active peptides would result. The knowledge of one skilled in the art as illustrated by Geysen therefore represents a method of contacting a sample with necessarily different single-sequence peptide rods in identifying antigenically active peptides.

Thus, the use of multiple probes in an art-known method such as that illustrated in Geysen would obfuscate the results of the analysis. The Federal Circuit has held that prior art which would "discourage" the ordinarily skilled artisan from attempting the claimed invention cannot validly support a rejection under 35 U.S.C. § 103. *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 16 USPQ2d 1923 (Fed. Cir. 1990). Moreover, as also discussed above, use of two or more subpopulations would render the method illustrated in Geysen ineffective. If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984); MPEP § 2143.01. Accordingly, the incentive to combine the teachings of Walt et al. with knowledge in the art exemplified in Geysen is not provided in any of the cited references. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990).

B

In view of the above, Applicants submit that the claims are not obvious over Walt et al. in view of the knowledge available to one skilled in the art as illustrated in Geysen. Accordingly, Applicants respectfully request the Examiner to withdraw this rejection.

CONCLUSION

Applicants submit that the claims are now in condition for allowance and an early notification of such is solicited. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON & HERBERT, LLP

Date: 8/7/01

By: Robin M. Silva
~~David C. Foster, Reg. No. 44,685~~
~~Patent Agent for~~
Robin M. Silva, Reg. No. 38,304

Suite 3400, Four Embarcadero Center
San Francisco, California 94111-4187
Telephone: (415) 781-1989

1043999

B

RECEIVED
AUG 15 2001
TECH CENTER 1600/2900
OIPE
AUG 13 2001
PATENT & TRADEMARK OFFICE

Version with markings to show changes made

In the Claims

Please amend the claims as follows:

- - 18. (Amended) A method of determining the presence of one or more target analytes in one or more samples comprising:

a) contacting said sample with a composition comprising:

i) a substrate with a surface comprising a plurality of assay locations, each assay location comprising **a plurality of** discrete sites; and

ii) a population of microspheres comprising at least a first and a second subpopulation each comprising a bioactive agent;

wherein said microspheres are distributed on said surface such that said discrete sites **each** contain **no more than one microsphere** [microspheres]; and

b) determining the presence or absence of said target analyte.

19. (Amended) A method of determining the presence of one or more target analytes in one or more samples comprising:

a) adding said sample to a first substrate comprising a plurality of assay locations, such that said sample is contained at a plurality of said assay locations;

b) contacting said sample with a second substrate comprising:

i) a surface comprising a plurality of array locations, each array location comprising **a plurality of** discrete sites**, wherein at least one assay location is in fluid contact with at least one array location**; and

ii) a population of microspheres comprising at least a first and a second subpopulation each comprising a bioactive agent;

wherein said microspheres are distributed on said surface such that said discrete sites **each** contain **no more than one microsphere** [microspheres]; and

c) [b)] determining the presence or absence of said target analyte.

20. (Amended) A method according to claim 18 wherein each of said assay locations comprises a **library** [substantially similar set] of bioactive agents.

21. A method according to claim 18 wherein said substrate is a microtiter plate and each assay location is a microtiter well.

22. A method according to claim 18 wherein each discrete site is a bead well.

23. A method according to claim 18 wherein each of said subpopulations further comprise an optical signature capable of identifying said bioactive agent.

24. (Amended) A method according to claim 18 wherein [each] **at least a first and second microsphere in** [of] said subpopulations further comprise an identifier binding ligand that will bind a decoder binding ligand**, whereby said bioactive agent is identified by said identifier**

B

binding ligand binding to said d coder binding ligand [such that the identification of the bioactive agent can be elucidated].

25. A method according to claim 19 wherein said first substrate is a microtiter plate.

26. A method according to claim 19 or 25 wherein said second substrate comprises a plurality of fiber optic bundles comprising a plurality of individual fibers, each bundle comprising an array location, and each individual fiber comprising a bead well.

27. A method according to claim 19 wherein each of said subpopulations further comprise an optical signature capable of identifying said bioactive agent.

28. A method according to claim 19 wherein each of said subpopulations further comprise an identifier binding ligand that will bind a decoder binding ligand such that the identification of the bioactive agent can be elucidated.

29. A method according to claim 18 or 19 at least one of said target analytes is a nucleic acid.

30. A method according to claim 18 or 19, wherein said microspheres are randomly distributed on said surface.

31. A method according to claim 18 or 19, wherein at least a first subpopulation of microspheres comprises a bioactive agent comprising nucleic acids.

32. A method according to claim 18 or 19, wherein at least a first subpopulation of microspheres comprises a bioactive agent comprising a protein.

33. (New) A method according to claim 20, wherein at least a first and second of said assay locations comprise the same library of bioactive agents.

34. (New) A method according to claim 20, wherein at least a first and second of said assay locations comprise different libraries of bioactive agents.